High-Flow Nasal Cannula Oxygenation in Immunocompromised Patients With Acute Hypoxemic Respiratory Failure: A Groupe de Recherche Respiratoire en Réanimation Onco-Hématologique Study

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Drs. Lemiale, Azoulay, Resche-Rigon, and Chevret designed the study, made statistics, and wrote the article. Drs. Lemiale, Mokart, Pène, Argaud, Mayaux, Guitton, Rabbat, Girault, Kouatchet, Vincent, Bruneel, Nyunga, Seguin, Klouche, Colin, Kontar, Perez, Meert, Benoit, and Papazian included the patients and acquired the data. Drs. Lemiale, Azoulay, and Resche-Rigon analyzed and interpreted the data. Drs. Lemiale, Demoule, and Azoulay drafted the article. All the authors reviewed the article and revised it critically for important intellectual content. All authors approved the final version to be published.

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Objective: In immunocompromised patients with acute respiratory failure, invasive mechanical ventilation remains associated with high mortality. Choosing the adequate oxygenation strategy is of the utmost importance in that setting. High-flow nasal oxygen has recently shown survival benefits in unselected patients with acute respiratory failure. The objective was to assess outcomes of immunocompromised patients with hypoxemic acute respiratory failure treated with high-flow nasal oxygen.

Design: We performed a post hoc analysis of a randomized controlled trial of noninvasive ventilation in critically ill immunocompromised patients with hypoxemic acute respiratory failure.

Setting: Twenty-nine ICUs in France and Belgium.
Patients: Critically ill immunocompromised patients with hypoxemic acute respiratory failure.
Intervention: A propensity score–based approach was used to assess the impact of high-flow nasal oxygen compared with standard oxygen on day 28 mortality.
Measurements and Main Results: Among 374 patients included in the study, 353 met inclusion criteria. Underlying disease included mostly malignancies ($n = 296$; 84%). Acute respiratory failure etiologies were mostly pneumonia ($n = 157$; 44.4%) or opportunistic infection ($n = 76$; 21.5%). Noninvasive ventilation was administered to 180 patients (51%). Invasive mechanical ventilation was ultimately needed in 142 patients (40.2%). Day 28 mortality was 22.6% (80 deaths). Throughout the ICU stay, 127 patients (36%) received high-flow nasal oxygen whereas 226 patients received standard oxygen. Ninety patients in each group (high-flow nasal oxygen or standard oxygen) were matched according to the propensity score, including 91 of 180 (51%) who received noninvasive ventilation. High-flow nasal oxygen was neither associated with a lower intubation rate (hazard ratio, 0.42; 95% CI, 0.11–1.61; $p = 0.2$) nor day 28 mortality (hazard ratio, 0.80; 95% CI, 0.45–1.42; $p = 0.45$).
Conclusions: In immunocompromised patients with hypoxemic acute respiratory failure, high-flow nasal oxygen when compared with standard oxygen did not reduce intubation or survival rates. However, these results could be due to low statistical power or unknown confounders associated with the subgroup analysis. A randomized trial is needed. (*Crit Care Med* 2017; 45:e274–e280)
Key Words: immunosuppression; leukemia; lymphoma; neutropenia; noninvasive ventilation; mechanical ventilation

Acute respiratory failure (ARF) remains the first reason for admission to ICU in immunocompromised patient (1–3). Various etiologies lead to ARF in that setting. Among predictors of outcomes, mechanical ventilation remains the major determinant of death (4–7). Thus, optimal adequate oxygenation strategy must be selected as early as possible, to avoid invasive mechanical ventilation. Fifteen years ago, noninvasive ventilation (NIV) was associated in decreased need for intubation and reduced mortality (8). However, most recent studies did not confirm these results (9). Recently, high-flow nasal oxygen (HFNO) has proven benefit in unselected patients with hypoxemic ARF. HFNO allowed decreasing intubation in the most hypoxemic patient. Furthermore, this device was associated with a significant decrease in mortality (10). However, in immunocompromised patients, prospective data are lacking. In a retrospective study with 178 cancer patients with hypoxemic ARF, HFNO plus NIV was compared with standard oxygen or NIV alone (11). Although intubation rate was not different (47% vs 49%), mortality in patients receiving HFNO plus NIV was significantly reduced (37% vs 54%; $p = 0.027$). Last, unlike unselected patients, in a prospective multicentric randomized study including 100 immunocompromised patients with hypoxemic ARF, comfort was not improved using HFNO when compared with standard oxygen through the Venturi mask (12).

We performed a post hoc analysis of a randomized controlled trial of NIV versus standard oxygen in 374 immunocompromised patients admitted to ICU with ARF. The use of HFNO was left to clinician's decision. The aim of the present study was to assess the impact of HFNO on the need for intubation and on day 28 (D-28) mortality.

PATIENTS AND METHODS

Data Source

This study is a post hoc analysis of a randomized trial of NIV in 374 immunocompromised patients admitted to ICU with ARF (9). This trial was prospectively performed between August 5, 2013, and January 31, 2015, in 29 ICUs in France and Belgium. The study protocol was approved by the French Ethics Committee CPP Ile de France IV Saint Louis (ref number 2012/11SC). Informed consent was obtained from all patients. Exclusion criteria for this study were chronic respiratory failure, isolated cardiogenic edema, more than one organ failure and do-not-intubated order. HFNO could be used as oxygen device in the two groups and was not controlled. Data were prospectively and daily collected from admission to day 28. D-28 mortality was the primary outcome in this study and was available for all patients.

Selection of the Study Population for This Post Hoc Analysis

Among the 374 patients, those who stayed more than 2 days were included in the present analysis. Variables reported in tables and figures were collected prospectively. In particular, we analyzed all data previously identified as associated with mortality (underlying disease, performance status in the 3 mo from ICU admission, malignancy status [remission or not], ARF etiology, severity of organ dysfunction), and variables previously associated with the need of invasive mechanical intubation (oxygen flow at admission and severity of ARF, i.e., respiratory rate and Spo_2 at admission and in the first three ICU days) (13). Patients were categorized as HFNO patients if they had received HFNO within the first 2 days of ICU admission.

Using pre-established diagnostic criteria (14), investigators classified patients as having bacterial pneumonia, cardiac pulmonary edema, opportunistic pulmonary infections (including pneumocystis pneumonia and viral pneumonia), fungal pulmonary infections (mostly pulmonary invasive aspergillosis), or other ARF etiologies (including drug-related toxicity, infiltration related to hematologic disease, extrapulmonary acute respiratory distress syndrome [ARDS], and no definitive diagnosis). Patients were deemed to have an undetermined ARF etiology when no cause of ARF could be clinically or microbiologically documented (14), despite a comprehensive diagnostic workup. Corrected Sequential Organ Failure Assessment (SOFAc) score at admission was calculated without the respiratory components of the SOFA score.

Statistical Analyses

All data are presented as medians (25th–75th percentiles) for quantitative variables and frequencies (percentage) for qualitative variables. Baseline characteristics were compared between survival and dead patients using Wilcoxon rank-sum test for quantitative variables and Fisher exact test for qualitative variable.

A propensity score–based approach was used to limit bias of between-group comparison to assess the impact of HFNO when compared with standard oxygen on D-28 mortality (15). The propensity score was defined as the probability that a patient with specific baseline characteristics receive HFNO trial. Then, two patients with identical propensity score value but in the two different treatment groups (HFNO vs standard oxygen) can be considered as comparable, and matching on the propensity score has been shown as one of the most efficient method for treatment effect assessment (16, 17). We computed the propensity score using logistic regression to predict HFNO/standard oxygen group based on baseline characteristics known to be linked to the mortality (underlying disease, performance status more than 2 [dependent or bedridden], time between hospital and ICU admission, and allogeneic stem cell transplantation) (5, 18) and characteristics known to be linked to the intubation risk (respiratory rate, Spo_2, oxygen flow, and number of quadrant involved on chest x-ray at admission) and randomization group (NIV or oxygen only) (9). Standardized differences are used to compare balance in baseline covariates between two HFNO and standard oxygen groups (19). A 1:1 matching algorithm without replacement was used within a given range of 0.20 SDs of the logit of the estimated propensity score (15). Final analyses on the matched dataset were performed using Cox models with a random effect taking into account the paired observations except for ICU-acquired infection analyzed with a logistic model with random effect. Results were presented as hazard ratios or Odds-Ratio (OR) with their 95% CI. All tests were two sided at the 0.05 significance level. Analyses were performed using R version 3.1.2 (http://www.R-project.org).

RESULTS

Among 374 patients included in the primary study, 353 patients who stayed more than 2 days in ICU were included in the present analysis (**Fig. 1**). As shown in **Table 1**, the main underlying disease was cancer (n = 296; 84%), including 157 active malignancies (45.0%). Time between symptom onset and ICU admission was 1 day (0–2 d). Final ARF etiology was bacterial infections (n = 152; 43.1%), opportunistic infection (n = 76; 21.5), cardiogenic edema (n = 9; 2.5%), invasive fungal infection (n = 9; 2.5%), lung involvement by the underlying disease (n = 35; 9.9%), drug-related pulmonary toxicity (n = 19; 5.4%), extrapulmonary ARDS (n = 19, 5.4%), and miscellaneous diagnoses (n = 18, 5.0%). For 16 patients(4.5%), no diagnosis was determined after a complete diagnostic workup. At least, one investigation was performed for each patient, including bronchoalveolar lavage for 216 patients (61.5%).

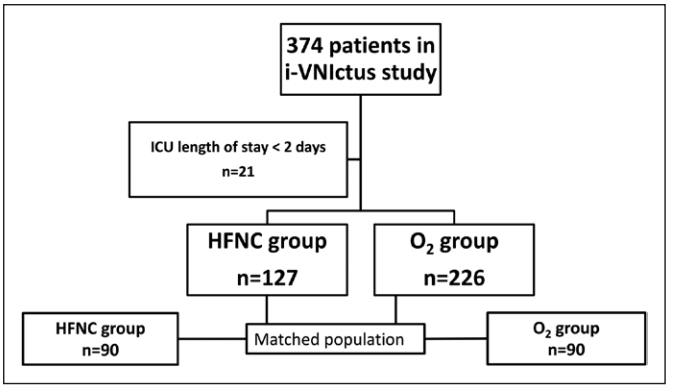

Figure 1. Patient diagram. HFNC = high-flow nasal cannula. O_2 = oxygen.

At admission 153 patients(43.3%) needed standard oxygen, at a flow over 9 L/min to maintain a Spo_2 of 96 (94–98). Respiratory rate at admission was 26 (21–30)/min. During the first 2 days, 127 patients(35.9%) received HFNO and 226 patients(64.0%) received standard oxygen. One hundred and eighty patients(51%) received NIV sessions. At admission, patients in the HFNO group had lower performance status than other patients. ARF related to bacterial infections were more frequent in the standard oxygen group, whereas invasive fungal infections and cardiac pulmonary edema were more frequently in the HFNO group (p = 0.005). SOFAc score was higher in HFNO group (p = 0.003). NIV tended to be less frequently needed in the HFNO group (p = 0.07). Day-28 mortality was 22.6% (80 deaths) and was higher in the HFNO group than in the standard oxygen group (25.9% versus 20.7%; p = 0.23) (Table 1). Overall, invasive mechanical ventilation was required in 57 patients (44.9%) from the HFNO group and 85 patients(37.6%) from the oxygen group, p = 0.21. Among them, overall length of ICU stay was 21 days (17–29 d). Table 1 describes intubation rate, ICU length of stay, and ICU-acquired infection rate in the two groups. Mortality rates of intubated patients (49% in HNFO group vs 42%; p = 0.33) were not different between the two groups.

One hundred and eighty patients (90 patients in the HFNO and 90 in the standard oxygen group) were included in the propensity analysis (**Supplemental Table 1**, Supplemental Digital Content 1, http://links.lww.com/CCM/C159). Patients were not different except for oxygen flows delivered. Particularly ARF etiology and characteristic of respiratory failure (respiratory rate, Spo_2 and associated organ failure) at inclusion were not different. As shown in **Table 2**, **Figure 2**, and **Supplemental Figure 1** (Supplemental Digital Content 2, http://links.lww.com/CCM/C160; **legend**, Supplemental Digital Content 1, http://links.lww.com/CCM/C159), impact of HFNO was not significant in the matched population for D-28 mortality (hazard ratio [HR] = 0.80 [0.45–1.43]), intubation rate (HR = 0.42 [0.11–1.61]), ICU length of stay (p = 0.59), or the proportion of patients developing ICU-acquired infection (HR = 0.80 [0.39–1.66]). We performed a sensitivity analysis including age that did not modify the results. Furthermore, D-28 mortality of intubated patients was not different between the two groups (18 of 40 [45%] in HFNO group vs 19 of 48 [39.6%],

TABLE 1. Patients' Characteristics and Outcome According to Oxygenation Strategy

Variables	High-Flow Nasal Oxygen Group ($n = 127$)	O_2 Group ($n = 226$)	p
Baseline characteristics			
Age (yr) m, [interquartile range]	64 [53–72]	63 [52–70]	0.71
Gender male	85 (67)	124 (55)	0.04
Underlying disease			0.38
Acute hematological malignancy	60 (47.2)	94 (41.6)	
Chronic hematological malignancy	22 (17.3)	43 (19.0)	
Tumor	30 (23.6)	47 (20.8)	
Solid organ transplantation	8 (6.3)	16 (7.1)	
Other immunosuppression	7 (5.5)	26 (11.5)	
Allogenic stem cell transplantation	17 (18.8)	17 (18.9)	0.74
Performance status > 2 (severely disabled or bedridden)	43 (47.7)	35 (38.8)	<0.001
Delay from respiratory symptoms to ICU admission (d)	1 [0–2]	1 [0–2]	.04
Neutropenia at admission	22 (28.2)	25 (33.3)	0.76
Acute respiratory failure etiology			0.005
Infection	51 (40.1)	101 (44.7)	
Cardiogenic edema	2 (1.6)	7 (3.1)	
Opportunistic infection	27 (21.2)	49 (21.6)	
Fungal infection	7 (5.5)	2 (0.9)	
Other[a]	40 (31.4)	67 (29.6)	
Maximum respiratory rate at day 1	26 [21–30]	25 [21–30]	0.5
Maximum O_2 flow at day 1	40 [15–50]	5 [4–9]	<0.001
Minimum Spo_2 at day 1	96 [93–97]	96 [94–98]	0.09
Noninvasive ventilation at day 1	56 (44)	124 (55)	0.07
Shock at day 1	21 (16)	32 (14)	0.66
Acute kidney injury at day 1	38 (30)	71 (31)	0.92
SOFA score at day 1 without respiratory	3 [1–5]	4 [2–6]	0.003
SOFA			
Bronchoalveolar lavage during ICU	47 (37)	88 (39)	0.76
Outcome			
Intubation throughout the ICU stay	57 (44.9)	85 (37.6)	0.21
Duration of mechanical ventilation	13 [4–46]	17 [7–33]	0.13
ICU length of stay	8 [5–16]	5 [2–40]	0.05
ICU-acquired infection	29 (22.8)	64 (28.3)	0.13
D-28 mortality	33 (25.9)	47 (20.7)	0.23
D-28 mortality of intubated patients	28/57 (49)	36/85 (42)	0.33

D-28 = day 28, SOFA = Sequential Organ Failure Assessment.

[a]Drug-related toxicity, infiltration related to hematologic disease, extrapulmonary acute respiratory distress syndrome, and no definitive diagnosis.

TABLE 2. Primary and Secondary Outcomes According to Oxygenation Strategy in the Matched Population

	High-Flow Nasal Oxygen Group ($n = 90$)	O_2 Group ($n = 90$)	Hazard Ratio 95% CI	p
Primary endpoint				
All cause 28-d mortality	21 (23.3%)	23 (25.5%)	0.80 (0.45–1.43)	0.45
Secondary endpoints				
Need for invasive mechanical ventilation	40 (44.4%)	48 (53.3%)	0.42 (0.11–1.61)	0.20
Duration of mechanical ventilation	13 [4–46]	16 [8–33]		0.32
ICU-acquired infection	21 (23.3%)	28 (31.1%)	0.80 (0.39–1.66)	0.55
Length of ICU stay	8 [5–16]	8 [3–29]		0.59
Length of hospital stay	24 [14–51]	32 [19–52]		0.25

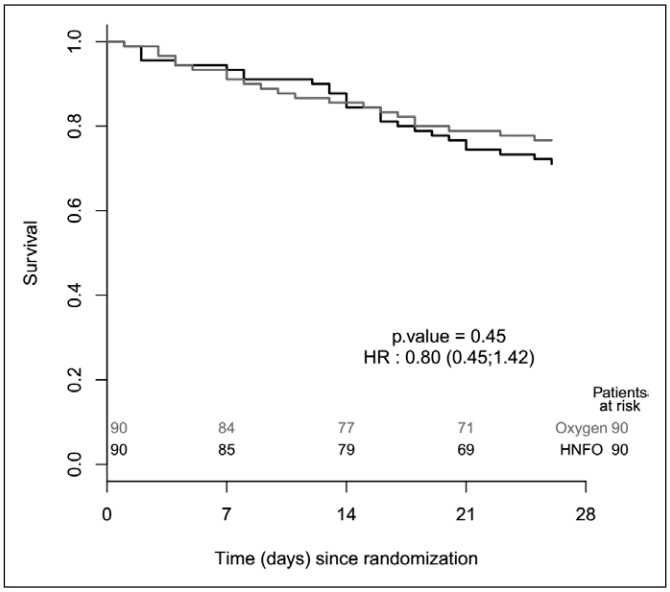

Figure 2. Probability of survival of the risk of day-28 mortality. Kaplan-Meier estimates of the probability of day-28 mortality in immunocompromised patients with acute respiratory failure receiving either high-flow nasal oxygen (HFNO) or oxygen. HFNO (*black line*), oxygen group (*gray line*).

odds ratio = 1.24 [0.53–2.92]; $p = 0.61$). Intubation rate and mortality according with the oxygenation strategy is described in **Supplemental Figure 2** (Supplemental Digital Content 3, http://links.lww.com/CCM/C161; **legend**, Supplemental Digital Content 1, http://links.lww.com/CCM/C159).

DISCUSSION

ARF is the leading cause for ICU admission in patients with hematological malignancies. Mortality of patients requiring mechanical ventilation remains high (5, 7, and 20), and every strategy that avoids intubation should be given priority. Previous studies have demonstrated benefits from NIV in immunocompromised patients with ARF at a time where mortality associated with mechanical ventilation was up to 80% (8). In more recent studies with lower mortality rates, NIV benefits could not be evidenced anymore (9). Recently, with the evidence that a new oxygen device as HFNO was associated with a decreased need of intubation in the most hypoxemic patients and reduced mortality rates in unselected critically ill patients with ARF, it is logical to establish whether or not these benefits extend to immunocompromised patients (10). In this study, including various types of immunocompromised patients, and analyzing only patients who received HFNO more than 2 days, HFNO was not associated with any significant benefits.

Interestingly, patients managed in this study have similar severity at ICU admission than those reported in previous studies (5, 20, 21). Also, even though intubation rate was similar when compared with that in earlier reports, mortality was lower (22% vs over 40%) than in previous studies, shedding light on continuing improvements in this population, even when patients are at high risk of receiving mechanical ventilation (5, 14, 22–25). Along this line, the use of ICU was made earlier in these patients (i.e., 1 d [0–2 d] after respiratory symptoms onset), as compared to previous studies (5, 26). Last, one may advocate that reported mortality rates are biased by inclusion and exclusion criteria that excluded patients with shock. However, the fact that patients with cardiac pulmonary edema for whom reported mortality is constantly lower, were also excluded may balance this bias (22, 27).

The research question pertaining to this study is whether or not ventilation strategy per se could have significant impact on outcomes. On the one hand, avoiding invasive mechanical ventilation and its complications carries obvious benefits. On the other hand, mortality of intubated patients has much decreased, whereas other determinants of mortality are still heavily impactful. Namely, delay in ICU management, ability to identify ARF etiology, invasive fungal infections, associated organ dysfunctions, and being allogeneic bone marrow transplant recipient are strongly associated with mortality (5, 18, 28). Whether initial oxygenation strategy might overcome these strong predictors of outcomes remains unclear. Unlike the Florali study (10) that mostly included unselected patients with community-acquired pneumonia, this study confirms that immunocompromised patients present with a wide spectrum of ARF etiology and that one strategy may not fit to all. Hence, the lack of benefit from HFNO may be

ascribable to a lack of adjustment on these important confounders, raising concerns on any generalizability of available data, and warranting dedicated trials in this specific population. Putting together these data and those from our NIV trial, we remind that delayed intubation had been associated with increased mortality in immunocompromised patients (26, 29, 30).

In keeping with our data, most of ARF etiologies were related to infections, a situation associated with higher mortality (22, 27, 31). Although mortality rate was low in our study, intubation rate in the matched population was over 40%, which depicts severe conditions. Furthermore less than 5% of patients remain without diagnosis of ARF. This proportion was lower than that of previous studies and was known to be associated with higher mortality rate (14, 23). This low mortality rate could be related to the admission of these patients in ICUs that are used to take care of immunocompromised patients with ARF (32).

This study has several limitations. First, this is a post hoc analysis of a prospective trial performed to demonstrate benefits from early NIV in immunocompromised patients with ARF (9). Nevertheless, randomization group was included in the propensity score and NIV may not have modified results. However, in a recent retrospective single-center study, treatment with NIV and HFNO was associated with a better survival in malignancy patients with ARF (11). Second, the decision to offer HFNO to ARF patients was left to physician in charge. Even though centers participating to this study have large experience of dealing with immunocompromised patients, no proper HFNO protocol was applied in this study. Furthermore, the study was performed before the HNFO trial was published (10). Thus, no standardized protocol for HFNO was described in the study. This was the most important weakness of this post hoc study. This propensity analysis with a matching procedure ensured to be as close as possible to a randomized clinical trial by selecting patients with comparable characteristics. For example, ARF etiologies were included in the matching procedure to consider length of pulmonary symptoms and severity of ARF in the propensity score. A trial to demonstrate survival benefits from HFNO comparing to oxygen remains warranted. Third, only 180 patients were included in the propensity analysis. This sample could be seen as small, but it was nearly as important as the sample in Florali study (106 patients in HNFC group vs 94 patients in oxygen group) (10). Furthermore this study was the most important in immunocompromised patients with ARF where mortality is higher than other patients.

In conclusion, in this post hoc analysis with immunocompromised patients and hypoxemic ARF, HFNO when compared with the standard oxygen did not reduce intubation or survival rates. However, these results could be due to low statistical power or unknown confounders associated with the subgroup analysis, a randomized trial is needed.

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